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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/739,223	Applicant(s) Batist et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *21 and 22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20 and 23-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of group I, claims 1-20 and 23-25, in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MEP. § 818.03(a)).

2. Claims 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 6.

Claims 1-25 are pending and claims 1-20 and 23-25 are under consideration.

Claim Rejections - 35 USC § 101

3. Claim 6 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. Claim 6 is directed to a method for a tumor-selective expression of a gene in a cell ***in vitro*** by using a gene construct comprising said gene operably linked to a tumor-specific rat Hex II promoter. The specification fails to assert a substantial and specific utility for a method of tumor-selective expression of a gene *in vitro*.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2, 3, 13-20 and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "LacZ or HSV Tk" in claim 2 is vague and renders the claim indefinite. It is unclear whether the LacZ or HSV Tk genes or proteins are intended. Claim 14 depends on claim 2 but fails to clarify the indefiniteness.

The phrase "a basic expression vector" in claims 3 and 15 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "a basic expression vector". The specification fails to specifically define the phrase "a basic expression vector". Claims 16-20 and 23-25 depend on those two claims but fail to clarify the indefiniteness.

Claims 13, 19 and 20 are indefinite because they refer to figures 1, 2 and 3, respectively. Claims must, under modern claim practice, stand alone to define invention, and incorporation into claims by express reference to specification and/or drawings is not permitted except in very limited circumstances; thus, claims in utility applications that define invention entirely by reference to specification and/or drawings, known as "omnibus" or "formal" claims, are properly rejected under 35 USC 112, paragraph 2, as failing to particularly point out and distinctly claim invention.

6. Claims 4, 17 and 18 provide for the use of a vector or a gene construct, but, since the claim does not set forth any steps involved in the method/process, it is unclear what

method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 4, 17 and 18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5 and 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumor cells by using a gene construct containing a HSV Tk gene under the control of a rat Hex II promoter *in vitro*, does not reasonably provide enablement for a method of a tumor-selective expression of a gene under the control of a rat Hex II promoter *in vivo* or a method of killing tumor cells by using a gene construct containing a HSV Tk gene or a cytochrome p450 gene and their respective prodrugs under the control of a rat Hex II promoter *in vivo*. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 5 and 7-12 are directed to a method for a tumor-selective expression of a gene in a cell comprising inserting a gene construct containing said gene and a rat HexII promoter into said cell, wherein said rat promoter is selectively activated in tumor cells as compared to normal cells. Claim 8 specifies the gene construct is inserted in an adenovirus type 5 vector or in a lipid-based delivery system. Claim 9-12 specify the gene encodes an enzyme, such as HSV Tk or cytochrome P-450, that converts a non-toxic prodrug into its active form, such as gancyclovir, cyclophosphamide, penicillin, amidase or β-lactamase.

The specification states "The invention relates to a novel tumor-specific promoter for use in gene targeted therapy that is differentially regulated in cancer cells, such as to drive a suicide gene in cancer therapy (see page 1, lines 14-17). The claims read on gene therapy *in vivo* in light of the specification. The specification only discloses the killing of tumor cells *in vitro* by using TK gene in combination with GCV, and higher expression activity of the rat Hex II promoter in mouse mammary carcinoma and human lung carcinoma cells as compared to mouse normal cells *in vivo*. Claims 5 and 7-12 encompass the use of various vectors such as retrovirus, adenovirus, plasmid, etc. in any kind of mammal including human beings for gene therapy in vivo via various administration routes.

The specification fails to provide adequate guidance and evidence that a tumor-selective expression of a gene under the control of a rat Hex II promoter would provide sufficient

expression of the gene product via various administration routes such that therapeutic effect can be obtained *in vivo* for a particular cancer cell. The specification also fails to provide adequate guidance and evidence that the combination of a toxic gene, such as HSV Tk gene or cytochrome p450 gene, and a prodrug under the control of a rat Hex II promoter would provide sufficient expression of the gene product via various administration routes such that therapeutic effect, such as inhibiting tumor cell growth or killing tumor cells, can be obtained *in vivo* for a particular cancer cell.

The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. The. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is

unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use a gene construct for tumor selective expression of a gene under the control of a rat Hex II promoter for gene therapy *in vivo* via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathupala et al., 1995 (The Journal of Biological Chemistry, Vol. 270, No. 28, p. 16918-16925, IDS-CA).

Claims 1-4, 15 and 18 are directed to a tumor-specific Hex II gene construct, such as a plasmid, an adenovirus type 5 vector or a lipid-based delivery system, comprising a rat HexII

promoter, wherein said promoter is selectively activated in tumor cells as compared to tumor cells. Claim 2 specifies the construct further comprises lacZ or HSV Tk.

Mathupala teaches higher level of type II hexokinase expression in AS-30D hepatoma cell line as compared to normal cells, and isolated and identified the sequence of the 4.3 kb promoter of type II hexokinase (Hex II promoter) from rat. Mathupala et al. also teach the construction of pGL2-luciferase containing Hex II promoter and pSV-β-galactosidase control vector to evaluate the activity of Hex II promoter by assaying the activities of luciferase and β-galactosidase (e.g. pages 16918, 16919). Thus, claims 1-4, 15 and 18 are anticipated by Mathupala.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-6, 8-20 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathupala et al., 1995 (The Journal of Biological Chemistry, Vol. 270, No. 28, p. 16918-16925, IDS-CA) in view of Stratford-Perricaudet et al., 1992 (IDS-CI), Osawa et al., 1996 (IDS-CE) and Martuza et al., US Patent No. 5,728,379 (IDS-AA) and further in view of Adams et al., 1995 (IDS-CB).

Claims 1-4, 13-20 and 23-25 are directed to a tumor-specific Hex II gene construct, such as a plasmid, an adenovirus type 5 vector or a lipid-based delivery system, comprising a rat HexII promoter, wherein said promoter is selectively activated in tumor cells as compared to tumor cells. Claim 2 specifies the construct further comprises lacZ or HSV Tk. Claim 16 specifies the Hex II promoter is provided in a negative orientation relative to a polycloning site. Claims 17 and 18 specify the gene construct is for use in selective expression of a gene in a human tumor cell and a non-human tumor cell, respectively. Claims 5, 6 and 8-12 are directed to a method for a tumor-selective expression of a gene in a cell comprising inserting a gene construct containing said gene and a rat HexII promoter into said cell, wherein said rat promoter is selectively activated in tumor cells as compared to normal cells. Claim 8 specifies the gene construct is inserted in an adenovirus type 5 vector or in a lipid-based delivery system. Claim 9-12 specify the gene encodes an enzyme, such as HSV Tk or cytochrome P-450, that converts a non-toxic prodrug into its active form, such as gancyclovir, cyclophosphamide, penicillin, amidase or β-lactamase.

Mathupala teaches higher level of type II hexokinase expression in AS-30D hepatoma cell line as compared to normal cells, and isolated and identified the sequence of the 4.3 kb promoter of type II hexokinase (Hex II promoter) from rat. Mathupala et al. also teach the construction of pGL2-luciferase containing Hex II promoter and pSV-β-galactosidase control vector to evaluate the activity of Hex II promoter by assaying the activities of luciferase and β-galactosidase (e.g. pages 16918, 16919).

Mathupala do not teach construction of adenoviral vector or plasmid vector containing CAT or HSV-TK gene, and expression of a gene under the control of a rat HexII promoter in human cells.

Stratford-Perricaudet et al. teach construction of a replication-deficient recombinant adenoviral plasmid pAdRSVβgal, lacking E1 region, under the control of RSV promoter and a recombinant adenovirus AdRSVβgal to inject intravenously or intramuscularly into mice for stable expression of β-galactosidase in mice (e.g. page 626).

Osawa et al. inserted rat HKII promoter (Hex II promoter) into BamHI site of a CAT reporter gene plasmid pCAT(An) to generate plasmid pHKIICAT(An)-1A (e.g. pages 17296, 17297). Osawa teach using the CAT reporter gene for the identification and characterization of cAMP-responsive element within the rat Hex II promoter.

Martuza teaches the use of HSV-TK gene and prodrug gancyclovir for virus-directed enzyme/prodrug therapy (VDEPT) and teach using replication-competent HSV that is capable of killing a specific target cell type or tumor cell *in vivo* by employing HSV that contains a tumor-, tissue- or cell-specific promoter operatively linked to an essential HSV gene (e.g. columns 2, 4).

Adams teaches increased hexokinase II expression in rat tumor cells such as hepatoma cells than in the rat normal counterpart, and also teaches increased hexokinase II expression in human renal carcinoma cells than in the human normal counterpart. Adams suggests that the observed increased hexokinase II expression in tumor cells may be a ubiquitous phenomenon during the malignant transformation (e.g. p. 53, 54).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the β-galactosidase or luciferase reporter gene with another reporter gene such as CAT in a plasmid vector as taught by Osawa, or in an adenoviral vector as taught by Stratford-Perricaudet, for the expression of said reporter gene under the control of a rat Hex II promoter. It would have been obvious for one ordinary skill in the art at the time of the invention to substitute the β-galactosidase or luciferase reporter gene with the HSV-Tk gene as taught by Martuza in an adenoviral vector as taught by Stratford-Perricaudet for the expression of HSV-Tk gene under the control of a rat Hex II promoter. It also would have been obvious for one ordinary skill at the time of the invention to substitute the β-galactosidase or luciferase gene with the CAT gene because they were known in the art as reporter genes for determining the activity of a promoter/enhancer.

One having ordinary skill at the time the invention was made would have been motivated to substitute the β-galactosidase or luciferase reporter gene with another reporter gene such as CAT in a plasmid vector as taught by Osawa or in an adenoviral vector as taught by Stratford-Perricaudet because known reporter genes would have been recognized by the ordinary artisan as being interchangeable, and one having ordinary skill would have been motivated to evaluate the activity of the Hex II promoter in normal cells and tumor cells by assaying for CAT activity. One having ordinary skill in the art would also have been motivated to substitute the β-galactosidase or luciferase reporter gene with the HSV-Tk gene as taught by Martuza in a plasmid vector, or in an adenoviral vector as taught by Stratford-Perricaudet, under the tumor-specific rat Hex II

promoter in order to express sufficient HSV-TK protein in specific tumor cells such that the tumor cells would have been killed when combined with prodrug gancyclovir for cancer gene therapy. One having ordinary skill at the time the invention was made would have been motivated to substitute the rat cells as taught by Mathupala with human cells as taught by Adams to study the activity of the rat Hex II promoter in normal human cells and human tumor cells so as to determine whether the rat Hex II promoter is more active in human tumor cells than in human normal cells because it was known in the art that the rat Hex II promoter is more active in tumor rat cells than in normal rat cells (Mathupala et al.).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S. Chen